

### REMARKS

The present invention relates in part to carrier solutions for the delivery and removal of cryoprotectants to cells, tissues, and organs. Prior to the present communication, Claims 1-9 were pending in the instant application. By the present submission, Applicant has cancelled Claim 5, amended Claims 1-4 and 7-9, and added new Claims 10-23. Notwithstanding the foregoing, Applicant expressly reserves the right to pursue subject matter no longer claimed in the instant application in one or more applications which may claim priority hereto.

Applicants note that the Examiner has indicated that dependent Claim 6 as originally filed is free of the art of record; the subject matter of this claim is now submitted as new independent Claim 21. The remaining new and amended claims do not introduce new matter or require a new search. For the convenience of the Examiner, the following table describes exemplary support for the various amendments.

<u>Amendment</u>	<u>Exemplary support</u>
Use of bicarbonate in the claimed solutions	Page 12, lines 18-22
Use of specific tonicity ranges	Page 12, lines 26-28
Use of glucose, mannitol, and lactose in the claimed solutions	Page 7, lines 19-25; page 12, lines 18-22
Use of potassium phosphate, calcium chloride, magnesium chloride, reduced glutathione, potassium chloride, sodium bicarbonate, and adenine in the claimed solutions	Page 12, lines 15-22
Use of solutions that do not cause osmotic volume changes of said cell, tissue or organ	Definition of "isotonic" U.S. Patent Application No. 09/916,032 (e.g., US 2002/0042042, paragraph 0031), which is incorporated by reference on page 3, lines 17-19; and in the art (see, e.g., <i>Dictionary of Cell Biology</i> , 2 <sup>nd</sup> Ed., Lackie and Dow, eds., 1995, provided herewith)

Applicant respectfully requests reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

*Non Art-Related Remarks*

Objections to the Specification

Applicants provide herewith a replacement specification incorporating changes requested by the Examiner. With regard to the terms used in Tables 2 and 3, the Examiner has also requested that Applicant indicate support for the various non-standard terms used. In this regard, the following summary is provided:

<u>Term</u>	<u>Exemplary support</u>
Wrcrit	Defined in table 2 legend
VEG	Defined in U.S. Patent Application No. 09/916,032 (e.g., US 2002/0042042, legend to Table 1), which is incorporated by reference on page 3, lines 17-19
D(1)F and D(.7)F	Defined in U.S. Patent Application No. 09/400,793 (e.g., US 6,395,467, legend to Table 6), which is incorporated by reference on page 3, lines 15-18
X1000	Defined in table 2 legend
PVP 5,000	Defined in table 2 legend
LM5	Defined at page 12, lines 18-22
K/Na(40), (30), and (20), and %K/Na: after -110°C	% of control potassium/sodium ratio as defined in table 2 legend; and in legend to table 6 in US 6,395,467
SEM	Defined in table 2 legend
DMSO	Defined in table 3 legend
Form.	Defined in table 3 legend

Acetol

Known in the art as  $\text{CH}_3\text{COCH}_2\text{OH}$

EG

Defined in table 3 legend

With regard to the term "Acetol," Applicants respectfully disagree with the Examiner that the term is open to various interpretations. As described in the *CRC Handbook of Physics and Chemistry*, Acetol is known in the art to refer to  $\text{CH}_3\text{COCH}_2\text{OH}$ , also known as hydroxyacetone and 1-hydroxy-2-propanone. For the convenience of the Examiner, an excerpt from this classic reference, listing Acetol as entry no. 325, is provided herewith. To the extent that the Merck Index indicates Acetol is also used as various proprietary names, Applicants submit that its use without capitalization in the instant specification indicates its use in its common form. *See, e.g.*, MPEP § 608.01(v).

35 U.S.C § 112, Second Paragraph

Applicant respectfully traverses the rejection of Claims 4-7 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the present invention.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed.Cir.1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed.Cir.1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.").

*Claims 4-7*

Applicant respectfully submits that the foregoing amendments to the claims render the rejections moot.

*Claim 5*

Claim 5 has been cancelled herein, rendering the rejection moot.

*Claim 7*

Applicant respectfully submits that the skilled artisan understands the meaning of the term isotonic to refer to solutions having a concentration that will not cause osmotic volume changes of cells immersed in the solution. For the Examiner's convenience, an excerpt from the *Dictionary of Cell Biology*, 2<sup>nd</sup> Ed., Lackie and Dow, eds., 1995, confirming this definition is provided herewith. This definition is entirely consistent with the definition of "isotonic" used in U.S. Patent Application No. 09/916,032 which is incorporated by reference in the instant specification on page 3, lines 17-19. *See, e.g.*, paragraph 0031, US 2002/0042042, a copy of which is provided herewith for the convenience of the Examiner.

The present specification uses this term in this context, *e.g.*, on page 12, lines 22-28. Furthermore, the effect of tonicity of cryoprotective solutions is described in detail in U.S. Patent Application No. 09/916,032. *See, e.g.*, Example 7 and accompanying figures and tables, US 2002/0042042. When read in light of the specification, the skilled artisan is reasonably apprised of the scope of the claims with regard to the scope of isotonic solutions.

In an effort to clarify the subject matter further for the benefit of the Examiner, Applicant has amended Claim 7 herein to refer to iostonic solutions as solutions that do not cause osmotic volume changes of the cell, tissue or organ referred to in the claim preamble. Applicant respectfully submits that the amendment made does not further limit the claims, nor should it be taken to do so. Applicant respectfully submits that the foregoing amendments render the rejection moot.

*Art-Related Remarks*

35 U.S.C. § 102

Applicant respectfully submits that the foregoing amendments to the claims render the rejection of Claims 1, 2, and 7 under 35 U.S.C. § 102(b) as allegedly being anticipated by Williams and Dean, *J. Parent. Sci.* 45: 94-100; or JP 01106826 moot. As amended herein, these claims distinguish over the cited publications in reciting solutions for the introduction and washout of cryoprotectants that comprise bicarbonate, mannitol, and lactose.

Nevertheless, Applicant respectfully disagrees with the Examiner's assertion that "[a]ny

liquid or solution is vitrifiable." Paper No. 10, page 4. The Examiner points with particularity to Ren *et al.*, *Cryogenics* 30(Suppl): 536-540 (1990) in efforts to support this assertion. Applicant notes that the Ren *et al.* publication actually states "Glass formation can be viewed as an intrinsic property of nearly any liquid" (emphasis added), a far less certain statement than that made by the Examiner. Furthermore, the ultrahigh cooling rates that may be required to vitrify many solutions may not be possible except in extremely small volumes that are inappropriate for the introduction and washout of vitrifiable concentrations of cryoprotectants in cells, tissues, and particularly organs. For example, adult organs may contain several hundred milliliters of liquid. The assertion that "any liquid or solution" is vitrifiable fails to consider that liquids may not be in an ideal environment for vitrification.

Applicant also respectfully disagrees with the Examiner's assertion that "mannitol and lactose are known to have cryoprotectant effects in the art." Paper No. 10, page 4. The Examiner points with particularity to U.S. Patent No. 5,879,875 in efforts to support this assertion. Applicant submits that no cryoprotectant effects for mannitol or lactose, either alone or in combination, are demonstrated or even alleged by the cited patent. Contrary to the Examiner's reading of this patent, the '875 patent indicates that mannitol and lactose may be used as components of "compositions... for preserving biological materials." '875 patent, column 2, lines 41-42. As described throughout the cited patent, these compositions are used above freezing temperatures, and when used below freezing temperatures, a cryoprotectant is suggested.

The suggested utility for the compositions in the '875 patent is to "isolate cells from external stimulatory signals carried through the cell membrane by preventing the opening of ion channels" ('875 patent, column 7, lines 35-40), a utility that has nothing to do with cryoprotection. While cryoprotectants may be discussed by the '875 patent (e.g., at column 1, line 66, through column 2, line 4), there is no suggestion that mannitol or lactose serve this function.

The rejected claims each refer to solutions comprising one or more cryoprotectants at certain effective concentrations. In the art, the term "cryoprotectant" refers to components of a solution that reduce or prevent the damage resulting from freezing of cells, tissues, or organs, typically by inhibiting ice crystal formation. Applicant respectfully submits that, at certain

concentrations, cryoprotectant solutions may not be vitrifiable. Moreover, to the extent that the Examiner implies that the term "cryoprotectant" as used in the art includes "pure water," Applicant respectfully submits that this is inconsistent with the meaning of the term in the art, as nothing in "pure water" reduces or prevents the damage resulting from freezing of biological material. Should the Examiner maintain the rejection, Applicant respectfully requests that the Examiner cite objective evidence to support the assertion that the cited publications disclose any solutions comprising a cryoprotectant at a vitrifiable concentration (*see, e.g.*, Claim 2), or in an amount sufficient for vitrification of a cell, tissue or organ (*see, e.g.*, Claims 14 and 19).

35 U.S.C. § 103

Applicant respectfully traverses the rejection of Claims 1, 2, and 7 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wiggins *et al.*, U.S. Patent No. 5,879,875 ("the '875 patent"); and claims 3, 4, and 5 as allegedly being unpatentable over the '875 patent in view of Fahy *et al.*, 6,395,467.

To establish a *prima facie* case of obviousness, three criteria must be met: there must be some motivation or suggestion, either in the cited references or in knowledge available to the ordinarily skilled artisan, to modify or combine the references; there must be a reasonable expectation of success in combining the references; and the references must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) *See also*, MPEP §2143.

As discussed above, the rejected claims, as amended herein, distinguish over the cited publications in reciting solutions for the introduction and washout of cryoprotectants that comprise bicarbonate, mannitol, and lactose. In contrast, Applicants respectfully submit that the '875 patent explicitly states that "univalent oxyanions" such as bicarbonate, are to be avoided in the disclosed "preservation" compositions. *See, e.g.*, '875 patent, column 6, lines 63-66 ("[i]ons, excluding univalent oxyanions and iodide, may be included in preservation solutions of the present invention"); *see also*, column 2, lines 45-53; column 6, lines 5-8; and each of the claims. Because the '875 patent teaches away from the solutions of the instant claims, no *prima facie* case of obviousness has been established. *See, e.g.*, MPEP § 2145(X) (a proposed modification cannot render prior art unsatisfactory for its intended purpose; it is improper to combine

publications when a publication teaches away from that combination; proceeding contrary to accepted wisdom is evidence of nonobviousness).

Moreover, the instant claims refer to compositions comprising specific components (*e.g.*, mannitol, lactose and bicarbonate in Claim 1). Nothing of record in the rejection indicates that these various components should be combined in the manner claimed. Describing the burden placed upon an examiner in establishing a *prima facie* case of obviousness, the Court of Appeals for the Federal Circuit has cautioned that:

[t]he factual inquiry whether to combine references of record must be thorough and searching. It must be based upon objective evidence of record.... [T]he best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.... [P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

*In re Sang-Su Lee*, 277 F.3d 1338, 1343 (2002) (internal citations omitted, emphasis added).

In the present case, the '875 publication indicates that solutions comprising "a first neutral solute with no net charge, having a molecular weight of at least about 335 and a solubility in water of at least about 0.3M; and a second neutral solute having a molecular weight of less than about 200, the second solute additionally having both hydrophilic and hydrophobic moieties" can be used to store cells. '875 patent, column 2, lines 45-53. While it may be true that lactose is a neutral solute with no net charge, having a molecular weight of at least about 335 and a solubility in water of at least about 0.3M, and mannitol is a neutral solute having a molecular weight of less than about 200 and both hydrophilic and hydrophobic moieties," the list of potential compositions meeting these limitations is potentially enormous. No exemplary compositions comprising both mannitol and lactose are disclosed in the '875 patent, and no exemplary compositions comprising either mannitol or lactose together with a cryoprotectant are disclosed in the '875 patent. Furthermore, as discussed above, no cryoprotectant effects for mannitol or lactose, either alone or in combination, are alleged or demonstrated by the cited patent.

Thus, the skilled artisan, seeking to provide solutions for introduction or washout of cryoprotectants, and having no knowledge of the instant specification, would not be motivated to

combine the components recited in the instant claims. In the absence of a motivation, based upon objective evidence of record, to combine and modify the cited publications to provide the claimed invention, no *prima facie* case of obviousness has been established.

Because no *prima facie* case of obviousness has been established with regard to the instant claims, Applicant respectfully requests that the rejections under 35 U.S.C. § 103 be reconsidered and withdrawn.


### CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully submits that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

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FOLEY & LARDNER  
P.O. Box 80278  
San Diego, CA 92138  
Telephone: 858-847-6700  
Facsimile: 858-792-6773

By   
For Stephen E. Reiter,  
Michael Whittaker  
Registration No. 46,230